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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,639	02/02/2004	Francisco Sanchez-Madrid	27331-501CIP2A	1583

30623 7590 03/26/2008

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
03/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/770,639	**Applicant(s)** SANCHEZ-MADRID ET AL.	
	Examiner ZACHARY SKELDING	**Art Unit** 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 February 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *15 February 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *56,59,60,67-69 and 105-108*.
   Claim(s) withdrawn from consideration: *70-77*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644

Continuation of 11. does NOT place the application in condition for allowance because:Applicant's after final amendment to the claims and remarks filed March 15, 2008 is acknowledged.

Claims 1-55, 57, 58, 61-66, 78-104 have been canceled.

Claim 59 has been amended.

Claims 56, 59, 60, 67-77 and 105-108 are pending.

Claims 56, 59, 60, 67-69 and 105-108 are under consideration as they read on a method of treating an unwanted immune response comprising administering a depleting anti-CD69 antibody, wherein the species of unwanted immune response is "rheumatoid arthritis".

Claims 70-77 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to non-elected inventions.

This Office Action is in response to applicant's amendment filed March 15, 2008.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 56, 59, 60, 67-69, 105 and 106-108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over McInnes et al. #1 (Immunol Today. 1998 Feb;19(2):75-9), in view of Ledbetter et al. (US 2003/0118592), McInnes et al. #2 (Nat Med. 1997 Feb;3(2):189-95), Feng et al. (Int. Immunol. 2002 Jun;14(6):535-44), Nakayama et al. (J. Immunol. 2002 Jan 1;168(1):87-94), Lauzurica et al. (Blood. 2000 Apr 1;95(7):2312-20) and Cheon et al. (Clin. Exp. Immunol. 2002 Mar;127(3):547-52), essentially for the reasons of record as put forth in the Office Action mailed August 18, 2007.

Applicant argues that McInnes 1998, McInnes 1997 and Ledbetter do not identify CD69 as a therapeutic target for the treatment of rheumatoid arthritis. Applicant further argues that the rationale for asserting that Ledbetter teaches depleting anti-CD69 antibodies is unclear and not supported by the proper documentary evidence. Applicant further argues that there is no motivation to combine McInnes 1998, McInnes 1997 and Ledbetter to arrive at the claimed invention, and that one of ordinary skill in the art would not have a reasonable expectation of success in combining these references to arrive at the claimed invention. Applicant maintains that the results of the instant specification unexpectedly show that an anti-CD69 antibody which down modulates CD69 from the T cell surface exacerbates disease symptoms in a murine collagen induced arthritis (CIA) model while a depleting anti-CD69 antibody significantly reduces CIA. Lastly, applicant asserts that in pointing to the teaching of Cheon the examiner is "conflating TGF-β and T-Cells with CD69. TGF-β, T-Cells and CD69 are all distinct compositions and play a distinct role in any normal or disease pathology."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 15, 2007.

With respect to the combined teachings of McInnes 1998, McInnes 1997 and Ledbetter Applicant's arguments that consider each reference individually, in very narrow contexts, fail to account for the fact that the skilled artisan does not work in a vacuum. In this instance the skilled artisan would simply note that the McInnes references teach that IL-15 mediates the recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients, that said IL-15 activated T cells rapidly upregulate CD69 expression, that these CD69+ T cells produce TNF-α and induce TNF-α production in monocytes/macrophage and that anti-CD69 antibodies block IL-15 activated T cell production/induction of TNFα in macrophage/monocytes. Thus, the reference teachings point one of ordinary skill in the art to three targets: the IL-15 ligand, the IL-15 receptor and CD69. Thus the applied references teach a limited number of therapeutic possibilities, any one of which would be predicted by one of ordinary skill in the art to useful in treating rheumatoid arthritis.

Moreover, McInnes 1998 teaches that "T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious." (see, in particular, sentence bridging pages 77-78). Thus, McInnes specifically directs one of ordinary skill in the art to a therapy that not only blocks T-cell activation but also depletes T cells from the synovial compartment as being most efficacious.

In this regard, it is noted that applicant's argument that this teaching "is inapposite to the current analysis. Here, McInnes 1998 is suggesting T-cell directed therapies that not only inhibit T-cell activation but also deplete T-cells from the synovial compartment. This is distinct from a method of administering a depleting anti-CD69 antibody such as in the methods now claimed," is not found convincing because it is unclear how a "T-cell directed therapies that not only inhibit T-cell activation but also deplete T-cells from the synovial compartment" fails to teach the use of a depleting anti-CD69 molecule.

With respect to the teachings of the Ledbetter, applicant argues the rationale for asserting Ledbetter teaches depleting anti-CD69

antibodies is unclear and not supported by the proper documentary evidence.

The Examiner's position is essentially as stated in the Final Office Action of August 18, 2007. Ledbetter teaches human and humanized anti-CD69 antibodies with antibody dependent cell cytotoxicity and complement fixation activity, both of which lead to effective depletion of immune cells, such as B cells and T cells, and that radiolabeled antibodies and toxin conjugated antibodies are effective for treating tumors, such as B cell tumors. As would be well known to one of ordinary skill in the art, radiolabeled antibodies and toxin conjugated antibodies deplete the cells to which they bind by killing them. Ledbetter further teaches that autoreactive T and B cells are present in rheumatoid arthritis patients, and claims various depleting antibodies, including anti-CD69 antibody, can be used to treat various autoimmune diseases and tumors, including rheumatoid arthritis.

Furthermore, the examiner submits that "proper documentary evidence" demonstrating that Ledbetter is indeed teaching antibodies that deplete cells via antibody dependent cell cytotoxicity and complement fixation activity can be found throughout Ledbetter, for example, pages 1-4, paragraphs [0004]-[0019] and page 11, paragraph [0095].

With respect to applicant's argument that there is no motivation to combine McInnes 1998, McInnes 1997 and Ledbetter to arrive at the claimed invention, and that one of ordinary skill in the art would not have a reasonable expectation of success in combining these references to arrive at the claimed invention, the examiner disagrees, essentially for the reasons of record put forth in the Final Office Action of August 18, 2007.

With respect to applicant's argument that the results of the instant specification unexpectedly show that an anti-CD69 antibody which down modulates CD69 from the T cell surface exacerbates disease symptoms in a murine collagen induced arthritis (CIA) model while a depleting anti-CD69 antibody significantly reduces CIA, the examiner disagrees, essentially for the reasons of record put forth in the Final Office Action of August 18, 2007.

Applicant's discovery that an anti-CD69 antibody that leads to the complete loss of CD69 expression on CD69 expressing cells but does not deplete said cells in vivo exacerbates murine collagen induced arthritis, while a depleting anti-CD69 antibody treats murine collagen induced arthritis, while surprising in the context of murine collagen induced arthritis, does not necessarily make the claimed invention surprising or unexpected.

First, it should be pointed out that McInnes #1 teaches that "T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious." (see, in particular, sentence bridging pages 77-78). Thus, McInnes specifically directs one of ordinary skill in the art to a therapy that not only blocks T-cell activation but also depletes T cells from the synovial compartment as being most efficacious.

Moreover, it should be noted that murine collagen-induced arthritis, may be, by definition, different from human rheumatoid arthritis in that even in the absence of a disease inducing antigen, cytokines such as IL-15, and associated IL-15-upregulated T cell surface molecules such as CD69, can initiate and sustain the production of inflammatory mediators, such as TNFα, as underscored by the teachings of McInnes #1 and #2 put forth above.

Applicant asserts that in pointing to the teaching of Cheon the examiner is "conflating TGF-β and T-Cells with CD69. TGF-β, T-Cells and CD69 are all distinct compositions and play a distinct role in any normal or disease pathology."

The examiner agrees that TGF-β, T-Cells and CD69 are all distinct compositions and play a distinct role in any normal or disease pathology. However, the examiner has not conflated "TGF-β and T-Cells with CD69" because these molecules are interrelated in the context of the teaching of applicant's specification and in the art. For example, the instant specification teaches at page 98, 4th paragraph to page 99, 1st paragraph:

"To ascertain the functional in vivo role of CD69 in autoimmune reactivity and inflammation, the behavior of CIA in CD69 deficient B6 mice was analyzed. An exacerbated form of CIA was observed in CD69-/- mice that correlated with collagen type II (CII) specific T and B cell responses, an increase in some inflammatory mediators, and diminished local TGF-β synthesis. Local blockade of TGF-β increased severity in wildtype but not CD69 deficient mice. In addition, in vitro engagement of CD69 induced the production of TGF-β1. These results strongly suggest that CD69 is a negative regulator of autoimmune reactivity through TGF-β synthesis.....In vivo treatment with anti-CD69 antibodies results in different effects depending on the anti-CD69 used. The antagonist 2.2 anti-CD69 mAb enhances the immune response, resulting in increased CIA severity and a more efficacious tumor rejection. The depleting 2.3 anti-CD69 antibody deletes CD69+ activated effector leukocytes, resulting in attenuated CIA. In addition, this antibody may directly eliminate CD69+tumors."

Moreover, the instant specification teaches at Example 6 on pages 104-105:

"The effect of in vivo treatment with anti-CD69 antibody has been analyzed using two different anti-CD69 antibodies, mAb 2.2 and mAb 2.3, in the CIA model in DBA1 wild type mice.

MAb 2.2 behaves in vitro as a non-depletor antibody. An IgG1, it is unable to bind complement and does not lyse CD69 expressing cells in an in vitro chromium assay (not shown). Furthermore, mAb 2.2 does not induce TGF-β synthesis in vitro in the absence of crosslinking (Esplugues et al. 2003. J. Exp. Med. 197:1093; Sancho et al. 2003. J. Clin. Invest. 112:872).

The effect of 2.2 anti-mouse CD69 antibody was analyzed in vivo in a model of CIA in DBA/1 mice. In vivo treatment with this antibody leads to the complete loss of expression of CD69 in populations that express the molecule, such as CD3hi thymocytes (FIG. 22)....However, the total thymocyte pool remains constant...This shows that mAb 2.2 does not mediate depletion of CD69+ cells in

vivo. Further studies show that mAb 2.2 removes CD69 from the cell surface, i.e., antagonizes by down-modulation of CD69.

The treatment of CIA-induced DBA/1 mice with mAb 2.2 significantly exacerbated CIA when administered at days 20 and 28 during the initiation of the secondary response (FIG. 23), in agreement with our results in CD69-deficient mice (FIG. 1).

Quantitative RT-PCR analysis of mRNA from isotype control treated and anti-CD69 mAb 2.2-treated wildtype mouse hind paws showed that levels of IL-1β were increased [25.0+/-9 to 58.4+/-8 units, $p<0.01$ (Mann-Whitney U test)] and TGF-β1 were decreased [56.5+/-13 to 18.2+/-8 units, $p<0.01$ (Mann-Whitney U test)]. Levels of IL-4, TNF, MCP-1, and IFN-gamma mRNA were unchanged (N=12 mice per group in two independent experiments. Results for each cytokine are normalized to GAPDH expression measured in parallel in each sample). The results show that down-modulation of CD69 by mAb 2.2 leads to decreased TGFβ mRNA, and increased IL1β mRNA levels, consistent with the observed exacerbation of inflammation."

Thus, the unexpected teachings of the instant specification that "strongly suggest CD69 is a negative regulator of autoimmune reactivity through TGF-β synthesis" (see ibid) may only be true in the context of the particular murine model of a T cell mediated autoimmune disease, CIA, disclosed in the instant specification but not in the context of human disease given the teachings of Cheon.

In conclusion, when Applicant's arguments and objective evidence, and the data in the instant specification are taken as a whole and weighed against the evidence supporting the prima facie case of unpatentabililty, the instant claims, by a preponderance of evidence, remain unpatentable over McInnes #1 in view of Ledbetter and McInnes #2 as evidenced by Feng, Nakayama, Lauzurica and Cheon. See M.P.E.P. § 716.01(d).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
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Zachary Skelding, Ph.D.
Patent Examiner
March 17, 2008